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Although child survival has improved substantially in the past 15 years, the decline in neonatal mortality (particularly deaths related to neonatal sepsis) has been more modest, which has contributed to the overall non-attainment of Millennium Development Goal 4 (to reduce child mortality).[1] WHO recommends admission to hospital for any young infant (neonates and those aged 28–59 days) with clinically severe infections.[2] However, access to hospital care and lack of willingness (mostly on the part of parents) to admit a young infant with possible bacterial infection are some of the many factors that have contributed to neonatal sepsis continuing to account for about 7% of all child mortality.

In *The Lancet Global Health*, Fatima Mir and colleagues report results from the Simplified Antibiotic Therapy Trial (SATT) in Pakistan,[3] in which three antibiotic regimens were compared for treatment of neonatal infections: procaine benzylpenicillin and gentamicin; amoxicillin and gentamicin; and procaine benzylpenicillin, gentamicin, and amoxicillin. These findings add to evidence already available from the AFRINEST and Projahnmo studies (table).[4,5] The findings of these three studies, which together provide data for more than 8500 young infants, show that a substantial proportion of neonatal infections can be managed in the community when referral is not possible. The individual and combined results of these trials show that simplified antibiotic regimens (which include oral amoxicillin) are equally effective when compared with the standard 7-day course of injectable penicillin and gentamicin.

SATT addresses some of the key limitations of the other two trials. First, 1083 (44%) of 2453 neonates enrolled in the study were aged 0–6 days, reflecting the substantial contribution of this age group to infection-related neonatal mortality.[6] Although Mir and colleagues do not present data for treatment outcomes separately for this age group, it is anticipated that a pooled analysis—including data from all three studies—would address this evidence gap. These results would be of great interest to public health professionals and policy makers. Second, in SATT, blood cultures were obtained from 2067 (84%) enrolled infants and tests for antimicrobial susceptibility were done in positive samples, which is very impressive for a community-based study. But, as Aristotle said, "The more you know, the more you don't know". Only 81 (4%) samples were positive for a pathogen: 18 (22%) were *Campylobacter* species; 13 (16%) were pseudomonads, 12 (15%) were enteric Gram-negative organisms, and eight (10%) were *Streptococcus pyogenes*. These results differ from those reported in multicentre hospital-based studies in developing countries, both in terms of culture positivity and the microbes isolated, which are not unexpected in such a study.[7,8] However, what is perplexing is the high

	SATT[3]	AFRINEST*[5]	Projahnmo[4]
Age 0–6 days	1083/2453 (44%)	1160/3564 (33%)	253/2490 (10%)
Male sex	1309/2453 (53%)	1901/3564 (53%)	1530/2490 (61%)
Weight-for-age <–2 SD	940/2453 (38%)	611/3564 (17%)	N/A
One clinical sign alone	2141/2453 (87%)	3111/3564 (87%)	1543/2490 (62%)
Fever			
Alone	905/2453 (37%)	N/A	584/2490 (23%)
In combination with other signs	1015/2453 (41%)	1648/3564 (46%)	1035/2490 (42%)
Severe chest indrawing			
Alone	717/2453 (29%)	N/A	791/2490 (32%)
In combination with other signs	818/2453 (33%)	1553/3564 (44%)	1478/2490 (59%)
Poor feeding			
Alone	356/2453 (15%)	N/A	131/2490 (5%)
In combination with other signs	606/2453 (25%)	578/3564 (16%)	920/2490 (37%)
Hypothermia			
Alone	144/2453 (6%)	N/A	34/2490 (1%)
In combination with other signs	233/2453 (9%)	191/3564 (5%)	52/2490 (2%)
Movement only when stimulated			
Alone	19/2453 (1%)	N/A	3/2490 (<1%)
In combination with other signs	122/2453 (5%)	99/3564 (3%)	57/2490 (2%)
Death within 7 days	28/2251 (1%)	35/2516 (1%)	28/2367 (1%)
Treatment failure	265/2251 (12%)	183/2516 (7%)	207/2367 (9%)
Admission	51/265 (19%)	8/183 (4%)	54/207 (26%)
Persistence of signs on day 4	62/265 (23%)	82/183 (45%)	34/207 (16%)
Appearance of new signs on or after day 3	22/265 (8%)	17/183 (9%)	21/207 (10%)
Recurrence of signs on or after day 5	44/265 (17%)	19/183 (10%)	37/207 (18%)
Treatment failure risk difference (95% CI)			
Arm B *vs* arm A*†	–1·9 (–5·1 to 1·3)	–1·9 (–4·4 to 0·1)	–1·5 (–4·3 to 1·3)
Arm C *vs* arm A‡	1·1 (–2·3 to 4·5)	–0·6 (–3·1 to 2·0)	–1·7 (–4·5 to 1·1)

Data are number of patients/total number of patients (%), unless otherwise indicated. N/A=not available. *Excludes 890 infants who were given gentamicin and oral amoxicillin for 2 days followed by oral amoxicillin for 5 days. †Difference between amoxicillin and gentamicin (arm B), and procaine benzylpenicillin and gentamicin (arm A). ‡Difference between procaine benzylpenicillin, gentamicin, and amoxicillin (arm C), and procaine benzylpenicillin and gentamicin (arm A).

Table: **Comparison of baseline characteristics and treatment outcomes in SATT, AFRINEST, and Projahnmo trials**

frequency of campylobacter bacteraemia (18/81 [22%]) noted (in the absence of diarrhoea) and bacteraemic treatment failure (9/18 [50%]), which has not been reported previously (even in the six-country study that includes this Pakistan study site).[8] This finding deserves further attention in future studies on the cause of neonatal sepsis.

Even though SATT and other studies have provided rich data with which to make an evidence-based decision about community management of neonatal infections using simplified antibiotic regimens, some concerns remain about this study. First, as in the other two trials, most children (2141/2453 [87%]) enrolled in SATT had only one of the five clinical signs of severe infection, which provides poor sensitivity (72%) and specificity (75%).[9] Additionally, only 1015 (41%) participants had fever in combination with another sign (this combination has a specificity of 92%).[9] This finding begs the question, did all participants have severe infection? Probably not, because case fatality was around 1% (28/2251 died within 7 days), which is very low even if participants with critical illness were excluded (ie, those at highest risk of death). Second, about a quarter of patients labelled as having treatment failure had persistence of clinical signs on day 4 (62/265 [23%]). This endpoint has not been shown to be a valid measure of treatment failure or poor prognosis and is likely to be subject to observer bias in such non-blinded studies. Third, although community health workers are good at screening young infants for referral, their specificity remains low (69%) compared with doctors (100%).[10] Therefore, at least 31% of the children in this trial might have received antibiotics unnecessarily. It is heartening to observe that 32 (86%) of 37 specimens tested for antimicrobial susceptibility were sensitive to amoxicillin and gentamicin. However, concerns about antibiotic overuse and resistance,[11] particularly to amoxicillin and gentamicin, are growing; these drugs are part of the simplified regimen.[7,8] Moreover, the frequency of surveillance visits noted in this study (ten over a 15-day period) are not attainable in programme settings, and results in practice are unlikely to be as impressive as those reported by Mir and colleagues. Therefore, until biomarkers (to reliably identify children with bacterial infections) that can be used by frontline health workers are developed, this strategy for community management of neonatal infections must be reserved for instances when referral is not possible.

Limitations notwithstanding, Mir and colleagues (along with the investigators in AFRINEST and Projahnmo) must be congratulated for successfully running a complex clinical trial to a high standard (with high rates of treatment adherence and follow-up). These studies represent a serious effort to address important but difficult clinical questions, with careful attention to a standardised study design and data quality. The findings of these trials show the need for continuing investment to develop point-of-care tests to identify children with bacterial infection at community or first-facility level, and for development of improved measures of treatment failure that are shown to be valid predictors of mortality or poor outcome. Until then, the challenge for policy makers today is to move forward based on a critical review of the best available data, such as these.

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